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# Dietary nitrates – to consume or to restrict?

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**Abstract**

**After years of concerns that nitrates present in the diet or water may cause cancer or birth defects, there are more and more reports inquiring that their consumption may, however, imply a number of health benefits. The impact of nitrates is related primarily to nitric oxide effects in individual cells and tissues. Double reduction, observed in $NO_3^- \rightarrow NO_2^- \rightarrow$ NO metabolic pathway, provides an alternative way of nitric oxide production, especially in ischemic or hypoxic conditions, when its obtaining from L-arginine is limited. Studies have shown that nitrate-rich diet improves bacteriostatic activity and positively impacts the cardiovascular system by increasing peripheral circulation and lowering systemic blood pressure. The relationship between nitrate intake and improvement of gastric epithelial function, mitochondrial metabolism and exercise tolerance was also confirmed. Although results of recent studies seem optimistic it has to be considered that most of them were conducted in a very small research groups and not all gave unequivocal results. So, to reliably answer the title question one still have to wait for more comprehensive research projects' results.**

**KEYWORDS: nitrite, nitrate, beetroot juice, mitochondrial metabolism, blood pressure, exercise oxygen uptake.**

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## Introduction

In the literature of recent years there are more and more reports on the impact of nitrates derived from water or food on the human body functioning. This impact particularly applies to the cardiovascular and digestive systems, mitochondrial efficiency and the improved level of metabolism and physical performance.

Metabolism of nitrates derived from the food occurs by $NO_3^- \rightarrow NO_2^- \rightarrow$ NO pathway, and therefore the physiological influence of nitrates is directly related to the of nitric oxide outcomes at the cellular and tissue levels. In the human body this pathway provides a specific security system of the nitric oxide production, particularly in ischemic or hypoxic states.

The aim of this paper was the literature review of the effects induced in the human body after consuming increased amounts of nitrates.

## Nitrite oxide

Nitric oxide (NO) is an unstable, lipophilic and poorly water-soluble gas, which, due to the chemical structure is a free radical [24, 29]. Basic pathways of nitric oxide creation and numerous transformations are shown in Figure 1. NO has a very short half-life, up to 30 seconds, in which it undergoes many biochemical transformations. Within the cytosol beside the oxidation to nitrite anion ($NO_2^-$), nitric oxide can react with proteins to form S-nitrosothiols or N-nitrosamines, eventually with superoxide anions ($O_2^{\bullet -}$) forming the highly oxidizing peroxynitrite (ONOO−) [29, 48]. Inside the red blood cells, with hemoglobin involvement, NO can be oxidized to form methemoglobin and nitrate

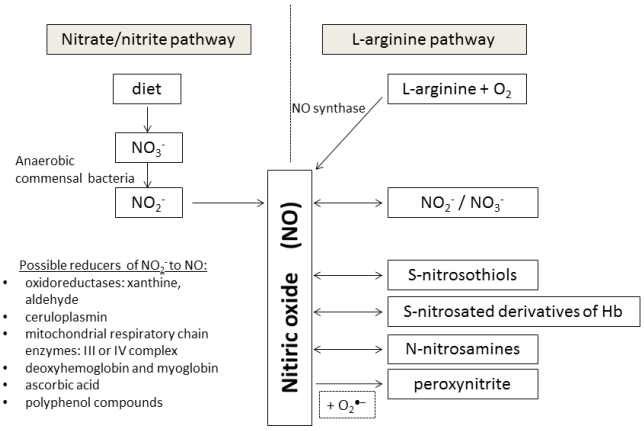


**Figure 1.** Biochemical pathways of nitric oxide creation and transformations

anion ($NO_3$) or S-nitrosated derivatives of hemoglobin [17, 48]. Nitric oxide can also be oxidized within the mitochondrion [53]. So many options of nitric oxide bioconversions suggests that the human body, in a fairly wide range, regulates the blood concentration of free nitric oxide.

Nitric oxide is endogenously produced predominantly from L-arginine, a relatively exogenous amino acid derived from food, intracellular protein degradation, or endogenous synthesis [29]. The group of nitric oxide synthase (NOS) enzymes catalyze the oxidation reaction of L-arginine imine group by molecular oxygen to produce L-citrulline and NO [29, 53]. Under hypoxic or acidic conditions such metabolic pathway becomes ineffective and nitric oxide–as needed–is released from previously filled reservoirs, primarily from S-nitrosoamines [48, 59]. The reduction of nitrite ions ($NO_2^-$) come to be a following significant endogenous source of nitric oxide. It can occur through several enzymatic and non-enzymatic pathways: with bacteria involvement, with the use of enzymatic nitrite reductases such as mitochondrial respiratory chain enzymes, hemoglobin or myoglobin, as well as other reducers such as ascorbic acid or polyphenol compounds [17, 19, 35, 49, 53]. Due to the possibility of two successive reduction reactions the pool of nitrates, to which are eventually oxidized unstable in whole blood nitrites, becomes another reservoir of nitric oxide [59].

In situation when impaired NOS activity and though limited filling of endogenous NO reservoirs (e.g. during hypoxia), the alternative for nitric oxide acquirement is the reduction of inorganic nitrates delivered with food or water [3, 35]. As shown in Figure 2 the intragastric pathway of NO generation from dietary nitrates (via entero-salivary circulation) includes several stages [41, 59]. After a meal rich in nitrates their level in plasma significantly increases. Most of $NO_3^-$ absorbed in the intestines is eventually excreted in the urine, yet up to 25% is actively retrieved from the blood by the salivary glands and are present in saliva [35]. In the oral cavity, commensal anaerobic bacteria reduce $NO_3^-$ to $NO_2^-$ [14, 22]. Next, nitrite-rich saliva enters the digestive tract, where in the acidic environment of stomach most of the $NO_2^-$ ions are reduced to nitric oxide [6, 37, 41]. The rate of this reaction is largely dependent on the concentration of the gastric reducing compounds such as: hemoglobin, ceruloplasmin, xanthine oxidant, ascorbic acid or polyphenols [37, 49]. The remaining part of the $NO_2$ ions is absorbed from the distal part of the digestive tract into the blood. The existence of the $NO_3^-\rightarrow NO_2^-\rightarrow$ NO metabolic pathway has also been demonstrated within the blood vessels, on the surface of the skin and in the urine [16, 39, 58].

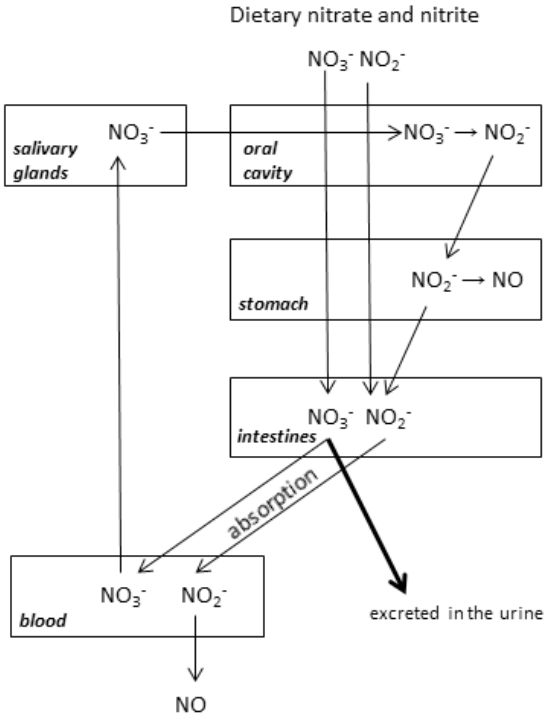


**Figure 2.** Dietary nitrate and nitrite transformation

## Dietary nitrate

Exogenous nitrates are delivered with diet: food and water. The main source of nitrates in the diet are vegetables, which can deliver up to 80-85% of dietary nitrate intake [10, 23, 35, 55]. Vegetables can be divided into three groups due to the amount of accumulated nitrate: containing small $NO_3^-$ amounts: peas, beans, tomatoes and cucumbers, moderate: carrots, parsley

and celery and large quantities: beetroot, lettuce, radish and spinach [23, 51]. The ability to accumulate nitrates in vegetables depends to a large extent on the intensity of fertilization, soil and climate conditions and the harvesting date. The accumulation of nitrates in the plants is conducive to a shorter vegetation period, cultivation on heavy soils, black soils and peat soils, low soil pH, fertilization (especially with nitrogen in nitrate form), low light intensity, and water shortage [51, 64]. EFSA (European Food Safety Authority) and WHO, European and global nutritional organizations, currently recommend Acceptable Daily Intake (ADI) at 3.7 mg $NO_3$/kg/day, which is equal to 222 mg daily for 60 kg human [40]. The nitrate intake depends very much on the composition of typical diet. According to the EFSA assessment [40] the nitrate intake in France was on average 141 mg per day and only 91 mg in the United Kingdom. It also confirms that the most important sources of nitrates in European diet are vegetables followed by fruits and water.

For many years it has been thought that nitrates and nitrites present in water or in food, especially in corned meat, cause many adverse alterations in humans. Studies conducted in 1960s and 1970s have shown that nitrates consumed with food, intensify the formation of N-nitrosamines, which can cause cancer, mainly stomach and large intestine cancer [10, 26, 62] or anemia (by hemoglobin oxidation to methemoglobin), which blocks the oxygen carrying function [26, 51, 62]. Most of these reports were related to animal models and their ambiguous results were not sufficient for extrapolation to humans. Nevertheless, after their publication, nitrates and nitrites used in the food industry have been identified by numerous state health authorities as being toxic, carcinogenic, teratogenic and mutagenic [9, 55]. As a consequence, in many countries, in the 1970s, limits on the content of these compounds in food and water were introduced [55]. Newer studies however largely contradict the original findings. As the consequence, among other actions, the World Health Organization has changed the regulations to significantly reduce the imposed limits [9, 26, 55, 62]. It is currently believed that only infants under four months of age, pregnant women and those suffering from advanced hypoxia (cardiovascular or respiratory disease, anemia) are at risk when excess nitrate supplementation may cause detrimental effects [40].

Epidemiological cohort studies indicate that there is no correlation between gastric malignant tumors morbidity and nitrate and nitrite consumption [9]. Multiple studies on the effects of diets rich in nitrates, conducted in the last 20 years, in addition to the lack of negative health consequences, show that, paradoxically, their intake may carry a number of positive effects on human beings. Most of them are directly related to nitric oxide influence [23, 36, 41], but the richness of antioxidants and other constituents with already proven health benefits [10, 40] contained in nitrate-rich vegetables and fruits are also of great matter.

**Effect of nitrate-rich diet on cardiovascular system**

Endothelial dysfunction, leading to the reduced nitric oxide bioavailability, is commonly recognized as an independent risk factor for atherosclerosis [13]. Nitric oxide, formed by the bioconversion of dietary nitrates exerts a preventive effect on cardiovascular disease. It is involved, inter alia, in inhibiting apoptosis of endothelial cells, aggregation and adhesion of leukocytes (especially platelets) to the endothelium surface, as well as in protective function against pathologic overgrowth of the endothelial layer [31, 58]. Empirical studies indicate that adequate NO levels also prevents excessive vasoconstriction (vasodilatory effect), thereby contributing to the prevention of cardiac events, particularly those with underlying hypertension [18, 31, 41, 58]. It has been proven that traditional Japanese nitrate-rich diet results in lower blood pressure levels compared to the control group on western diet, which in part explains why in Japan the morbidity rate for cardiovascular disease is relatively low [56].

Conclusions from recent original studies and numerous reviews indicate that dietary interventions targeted at increasing nitrate intake improve vascular endothelial function and mostly decrease systemic blood pressure in animals as well as in healthy and sick people [20, 31, 54, 57, 58]. There is, however, a considerable group of studies in which the blood pressure level after such intervention remained unchanged [7, 46, 61]. Such incoherent results are partly due to methodological differences in study protocols (sex, initial blood pressure level, nitrate dose, administration period), but may also indicate significant inter-individual variability of blood vessel reactivity to dietary nitrates [27, 63].

Beet root juice, except lowering central blood pressure, also increases the level of the distal arteries oxygenation. Three hours after consuming beet root juice patients with peripheral arterial disease (PAD) experience a substantial increase in exercise tolerance and duration to the intermittent claudication incidence [28]. Consumption of nitrates in the form of beet juice results also in improved brain microcirculation, which in turn plays a key role in cognitive and executive processes [44, 47, 60].

The reduction of nitrite within the cerebral cortex occurs, according to the model proposed by Millar [38], primarily with the involvement of the ascorbic acid present in significant amounts in nerve cells and astrocytes. In healthy adults, 90 minutes after ingestion of beet juice, when engaging cognitive functions the prefrontal cortex circulation improves significantly [60]. In the elderly, a two-day diet rich in nitrates affects the local improvement of brain critical areas blood supply, particularly the frontal lobe [47].

**Effect of nitrate-rich diet on digestive system functions**

Appropriate amount of nitric oxide in the gastrointestinal tract is essential to maintain normal gastrointestinal motility, mucosal blood flow, secretion of digestive juices and growth of gastric mucosa [11]. Numerous experimental studies have shown that nitrate supplementation supports the maintenance of normal NO concentrations within the gastrointestinal tract, resulting in increased gastric mucosal blood flow and secretion of mucus, while decreasing epithelial permeability [11, 36, 45]. Such nitrate properties underlie, among others, the reduction in gastric mucosal damage caused by the excessive intake of non-steroidal anti-inflammatory drugs, such as diclofenac [6, 45].
Gastroprotectional NO activity from entero-salivary circulation is also shown to reduce gastric mucosal inflammation and the risk of peptic ulcer disease [50, 52]. Bacteriostatic effects of nitric oxide produced by nitrite reduction in acidic environments have been confirmed, inter alia, for Salmonella, Yersinia, Shigella, Helicobacter pylori, Pseudomonas aeruginosa [16]. These effects are not limited to the gastrointestinal tract, they are also visible on the skin and in the urine [16, 41].

**Effect of dietary nitrates on mitochondrial metabolism**

Under hypoxia, nitric oxide originating from the reduction of $NO_2$ by myoglobin, blocks the binding possibility of oxygen to the respiratory chain complex III, causing its diffusion over the mitochondria into the tissues [53]. Though seemingly unfavorable, complex III blockade by NO may paradoxically contribute to the respiratory chain functioning improvement. In such a situation, a large functional reserve of cytochrome c oxidase is used, which allows the production of ATP without major losses [21]. When higher oxygen availability is returned, the respiratory chain recovers its primary function of oxygen management. These conclusions are confirmed by the results of studies by Larsen et al. when observing reduced oxygen uptake during exercise test in average-trained volunteers [34] and in the human mitochondria isolated from the vastus lateralis muscle [32]. Improvements in mitochondrial function are also necessary in situations of sudden onset of ischemia and subsequent reperfusion. This phenomenon occurs locally, for example, in hypoxia of the heart, liver, brain or kidneys or as a result of myocardial infarction. After a period of sudden ischemia and inhibition of the respiratory chain function, a reperfusion phase follows and allows the chain reactions of oxidation and reduction to occur. Reperfusion itself is associated with detrimental health consequences connected with the burst of reactive oxygen species (ROS) and the release of cytochrome c from mitochondria and initiation of apoptosis [53]. The nitrite administration, also as dietary supplement (whether used for 24 hours or 5 minutes before the ischemic episode) exhibit cytoprotective effect because it significantly reduces the negative consequences of reperfusion after hypoxia [8, 15, 53]. The possibility of direct limiting of the superoxide anion production may also contribute–to some extent–to inhibition of tissue inflammation, also developing under such conditions [53].

**Link between nitrate and nitrite with physical fitness and metabolism**

Research results on beneficial effects of increased nitrate supplementation on athlete's physical performance has led to introduction of beetroot juice into a list of reliable sports foods and supplement ingredients conducted by the Australian Institute of Sport (AIS). Since 2014 the beetroot juice is included in Group A of the AIS performance supplements list (used to directly contribute to optimal performance; commended for use under the supervision of appropriate sports medicine/science practitioner) [1]. During increased physical performance the reduced NO production of the classic metabolic pathway is due to the NOS enzymes inhibition (due to, inter alia, oxygen partial pressure reduction) or L-arginine deficiency (increased catabolic reactions and detoxication). Under such conditions, the alternative nitric oxide production pathway is activated: $NO_3^- \rightarrow NO_2^- \rightarrow NO$ [41, 59]. Majority of studies conducted so far, among sedentary and regularly-trained people, indicate that enriching the diet with nitrates induces an ergogenic effect.
Regardless of the given form (nitrate salts or beet root juice), nitrates, in most individuals, decrease oxygen uptake ($VO_2$) at a given level of exercise intensity. It corresponds to lower energy costs of exercise and increased exercise tolerance (shorter time of a certain distance coverage or longer distance covered at a certain time) [2, 5, 30, 34, 46]. It was also ascertained

that supplementation over the subsequent days does not further reduce $VO_2$ uptake, so there is no cumulative or adaptive effect of nitrate supplementation [57]. There are however, many publications not fully confirming physical capacity increment after nitrate intervention [4, 12, 43, 46, 61]. This condition can be explained by different research methodology or individual reactivity of study participants, but mostly by the research material selection. Prolonged regular physical activity results in the development of improved endogenous NO production – a specific adaptation confirmed by higher concentrations of nitrates and nitric oxide in athletes, both in resting and stress conditions [25]. It also seems probable that with higher sports level the nitrate supplementation becomes less significant, suggesting that in elite sportsmen the internal control of NO concentration is more effective and independent [4, 43, 61].

Reduced level of oxygen uptake during physical effort under nitrate-rich foods supplementation is associated with a lower metabolic rate in these conditions. This relationship was reported both in high and low intensity efforts [2, 30, 34]. In recent years, some trials have been carried out to test whether increased nitrate intake may also lead to decreased level of resting metabolism [42]. Although the results of these methodologically very different studies show a downward trend, are very ambiguous at the same time. One of the methodologically reliable analysis was carried out by Larsen et al. [33]. These authors found that after three days of $NaNO_3$ supplementation, in healthy young men, the level of primary metabolism decreased by 4.2%, regardless of insulin and thyroid hormone levels.

## Summary

This paper shows that nitrates, naturally present in Polish vegetables, have considerable biological and ergogenic potential. After years of doubts whether they threat a human health, it turns out that converted into nitrite and nitric oxide they exert a beneficial influence on body tissues, organs and energy expenditure. Importantly, the doses of nitrates needed to elicit the desired effects can be easily achieved by increasing the amount of vegetables like spinach, lettuce, beets or carrots in the daily diet.

Although the results of various research on the effects of nitrate compounds on the human body functioning are encouraging, it should be kept in mind that most of them were carried out in small research groups. Another limiting feature is that these analyzes focus on a limited amount of nitrate "carriers", that is to say they primarily concerned the consumption of nitrate salts or beetroot juice.

So, to reliably answer the title question whether person should eat or restrict dietary nitrates one have to wait for the results of more comprehensive research projects. It is important to evaluate the effects of nitrates in more people in different ages and in different health conditions, and whether other foods or juices containing nitrates generate a similar biological stimulus.

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